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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,164	12/20/2001	Benjamin J. Metcalf	33,484-00	3977

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,164	METCALF, BENJAMIN J.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11-12-04 has been entered.

The amendment and declaration filed 11-12-04 have been entered into the record. Claims 1-8 are pending and under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Maintained

Claims 1-8 are rejected under 35 USC 112, second paragraph as being indefinite for failing to particular point out and distinctly claim the subject matter which applicant regards as the invention for reasons made of record and new reasons set forth herein.

The rejection is withdrawn in part as it relates to the issue of the DNA not be able to be expressed in lipidated form. The claims recite the term "tightly regulated promoter". The term tightly is a measure of degree and comparison as previously set forth in the Office Actions of 11-25-03 and 5-13-04. The amendment of the specification attempts to resolve this issue by inserting "the recombinant PAL, under the control of said promoter is expressed in lipidated form and yields that are higher than those expressed by a recombinant pal that is not under the control of a tightly regulated promoter." This is insufficient to obviate this rejection. It now compares an unknown to an unknown and therefore the metes and bounds of "tightly regulated" is still a term of degree and is now complicated by being compared to an unknown value. Applicants submit a Declaration by

Susan Hoiseth that explains the terms as they are understood by a person of at least ordinary skill in the art. Declarant indicates a concurrence with the office's position that "tight" is a matter of degree and that tight promoters can also leak. So even tight promoters can leak to some degree and therefore the ability to leak, does not distinguish a tightly regulated promoter from one that is not. Leakiness is also a term of apparent degree. Neither the specification, nor the claims define "tightly regulated" such that one would be able to ascertain tightly regulated promoters based on some undefined degree of "leak". Minor leak referenced by Declarant is not defined in the specification nor compared in any means to other promoters that leak. Declarant defines the allegedly art understood terms, in yet more undefined terms of degree and concurs with the examiner that it is a term of degree (page 3, paragraph 7, line 3). Promoters that have leaks albeit, minor, major or something that falls in the middle are not clearly defined by the specification nor the claims. It is a term of comparison and a term of degree that does not readily apprise the skilled artisan of the endpoint of tightly regulated on the continuum of regulation or continuum of "leaky". If one were to consider regulation or "Leak" a continuum of degree of leakiness... from those that leak all the time to those that leak some of the time and those that do not leak, at what point on the continuum does a regulated promoter become "tightly regulated", what degree of leak is determined to be unacceptable for a "tightly regulated promoter"? This is not defined in the specification or the claims. Declarant points to page 8, lines 27-32 where Applicant constructed a plasmid to contain the arabinose inducible promoter because this promoter "is tightly regulated and almost completely inactive if no arabinose is present and some glucose is present". This is not persuasive. It describes at best a specific promoter and is not generalized to "tightly regulated" as is discussed in the specification page 12, lines 8-18, which broadly describes the characteristics of the recombinant systems as being regulatable. Further, it is apparent that there is some admitted leak from even the arabinose promoter. Therefore, there appear to be degrees of leak. Neither the

specification, nor the claims define the degree of leak that is acceptable for "tight promoters". It is not clear from either the specification or Declarant's opinion, where the boundary for leak exists, to define tight versus leaky. For the foregoing reasons, the rejection is maintained.

Further, as to claim 1, and dependent claims 2-8, the term "the recombinant PAL" lacks antecedent basis in the independent claim. Additionally, the comparison step is vague and indefinite because it does not compare the same proteins in the same system. For example, because the claim first uses "the recombinant PAL" which has no antecedent basis in the claims and then uses "a recombinant PAL", it is not clear what is being compared to what. The term "PAL" is a genus of proteins. The claim language as recited appears to compare any PAL with any other PAL in its genus and not against the identical protein produced under different conditions.

Claims 1, 2 and 8 are rejected under 35 USC 102(b) as being anticipated by Anilionis et al (WO 90/02557. published March 22, 1990) in light of Neslon et al (Infection and Immunity, 56(1):128-134, 1988) is maintained for reasons made of record.

Applicants arguments and the Declaration have been carefully considered but are not persuasive. Applicants argue that Anilionis et al does not teach the now recited function of comparison of levels produced from the plasmid in an undefined host cell system using an undefined basis for comparison. It would appear given the indefinite nature of the comparison, that absent the presence of the lac promoter of the art, that no protein would be produced from a recombinant host cell, and therefore the functional limitation is inherently met by the art. In other words, remove the lac promoter from the plasmid of Anilionis et al encoding a PAL protein of gram-negative bacterium and no protein would be produced in a host cell. The absence of the lac promoter (i.e. as it relates to "those expressed by a recombinant PAL that is not under the control of a tightly regulated promoter") would necessarily lead to no PAL protein expression. As such, given the

indefinite nature of the language of the claim, it appears removal of the argued "tight promoter" lac would necessarily lead to the recited function. Applicants admit that Anilionis discloses that PAL expressed from lac or PL promoters in *E. coli* JM103 or HB101 strains, only low levels were expressed. Applicants argue that Anilionis et al does not teach using a tight promoter to produce large amount of lipidated protein. This is not persuasive because the claims are not drawn to production of large amounts of lipidated protein. Therefore, in view of the recited interpretation of the functional language of the claim, the absence of the lack promoter, inherently leads to the function of not expressed in lipidated form and lower yields. Applicants argue that anticipation must be made based on a single reference and therefore addresses the rejection based on Anilionis alone and since Applicant himself states that P6 is also know as PBOMP-1, Nelson is of no moment and is irrelevant for this rejection. Nelson et al maybe be of no moment to Applicants but was used "in light of" to clearly demonstrate on the record that the same proteins were called by different names and therefore the Anilionis et al inherently met the claimed limitation of "P6" of *Haemophilus influenzae*. The teachings of Nelson et al are of moment to the rejection of the claims when Applicants use different nomenclature for the same protein.

The rejection is maintained.

The rejection of claims 3-5 under 35 USC 103(a) as being unpatentable over Anilionis et al (WO 90/02557, published March 22, 1990) in light of Neslon et al (Infection and Immunity, 56(1):128-134, 1988) as applied to claims 1, 2, and 8 above and in view of Guzman et al (Journal of Bacteriology, 177(14):4121-4130, 1995) is maintained for reasons made of record.

The rejection of claims 3 and 6 under 35 USC 103(a) as being unpatentable over Anilionis et al (WO 90/02557, published March 22, 1990) in light of Neslon et al

(Infection and Immunity, 56(1):128-134, 1988) as applied to claims 1, 2, and 8 above and in view of Mertens et al (Gene, 164:9-15. 1995) is maintained for reasons made of record.

The rejection of claims 3, 6 and 7 under 35 USC 103(a) as being unpatentable over Anilionis et al (WO 90/02557, published March 22, 1990) in light of Neslon et al (Infection and Immunity, 56(1):128-134, 1988) as applied to claims 1, 2, and 8 above and in view of Mertens et al (Gene, 164:9-15. 1995) and Novagen Inc, (admittedly commercially available in specification page 15, line 34) is maintained for reasons made of record.

Inasmuch as the 103 rejections have been traversed together they will be rebutted together. Applicants argue that Anilionis teaches that it is desirable to use strong promoters and that strong promoters are not equivalent to tightly regulated promoters. Declarant also attests to the finding that strong promoters are not equivalent to tightly regulated promoters. This is not persuasive, because it does not obviate the fact that Anilionis et al specifically teach that bacterial host cell strains and expression vectors maybe chose which inhibit action of the promote unless specifically induced (page 29, lines 27-30) and for purposes of expressing a cloned gene, it is desirable to use strong promoters in order to obtain a high transcription levels and hence expression of the gene. Anilionis et al teach depending upon the host cell system utilized any number of suitable promoters may be used (page 29, lines 10-15). The teachings of Anilionis et al provide for selection of a regulatable strong promoter. Each of Guzman et al, Mertens et al and Novagen Inc. provide promoters with these two characteristics. While the concept of strong promoters are not synonymous with tightly regulated promoters, this is not to say that some strong promoters are not tightly regulated. That is, the concepts are not mutually exclusive. The combination of strong promoter and regulation as specifically suggested by Anilionis et al is fulfilled by the promoters of the secondary reference that meet these functional limitations that are explicitly suggested by Anilionis et al. Strong promoters and tight regulatable promoters are not mutually exclusive. Applicants argue

the promoters specifically used by Anilionis et al are not tightly regulated. This is not persuasive, Applicants again argue the references individually and not as combined, using the specific suggestion explicitly recited by Anilionis et al. The secondary references as combined at the suggestion of the prior art meet the limitations of regulatable and strong promoters. There is no requirement that the art have the same rationale or motivation as Applicants to arrive at the claimed invention. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by Applicant. The name of the game is the claims, the dependent claims requires specific promoters an arabinose inducible or a T7 promoter in the claimed plasmid. The secondary art teaches that arabinose and T7 promoter fit the specific promoter selection criteria explicitly suggested by Anilionis et al. The fact that the arabinose promoter and T7 promoters are strong and regulatable are sufficient to meet the limitations of the claim. The fact that Applicants also describe or classify these identical regulated strong promoters as "tightly regulated" does not abrogate the fact that they also meet the functional criteria of suitable promoters as explicitly taught by Anilionis et al.

Applicants argue Nelson et al., Guzman et al, Mertens et al, and Novagen Inc piecemeal and not in combination. The advantages of the combination are explicitly provided for by Anilionis et al of record. The promoters of the secondary art of Guzman et al, Mertens et al, and Novagen Inc have those characteristics specifically suggested by Anilionis et al. Anilionis et al provides for the desirability of using promoters with these characteristics with the articulated expectation that these regulatable strong promoters would lead to a high level of transcription and hence a high level of expression of the gene. Therefore, Applicants are totally incorrect in that the art does not suggest the claimed combination as a solution for leading to higher expression (see page 29, lines 10-15, lines 27-30 of Anilionis et al). Even if the art did not expressly teach such, the art need not

provide the same motivation for making the combination as Applicants. Applicants continue to rely upon the increased expression of recombinant protein. This is not persuasive, the claims are drawn to a plasmid *per se* and not a method of making the recombinant PAL. The combination is suggested and enabled by the prior art combination. Applicants argue that the Examiner can not ignore that may laboratories tried and failed to express large amount of lipidated P6 and they all had the same references available to the Examiner to teach them how to do it. This is again not persuasive, these references are not of record and have not been provided to the examiner for independent evaluation of the evidence contained therein. Applicants aslo argue other references not before the examiner, again conclusions drawn by Applicants can not be independently evaluated because the references relied upon have not been provided for the record. Expression of lipidated rP6 was possible and was performed by the art and is acknowledged to be produced in Applicants previous response of record. The art explicitly suggests suitable promoter means for increasing quantities of the recombinant P6 protein. The art as combined teaches how to make the claimed plasmid for its intended use. The art as combined is functional for that intended use. The characteristics of the promoters of the secondary references are specifically taught by the art. Again, Applicants argue difficulties in the methods of production of the protein by other laboratories. This does not abrogate the fact that the lipidated P6, as acknowledged by Applicants, was in fact produced by the prior art. Applicants argue difficulties in achieving higher levels of production by other laboratories and this is not persuasive, because difficulties in a higher level of expression is not an indication of no expression or that the plasmids were not functional to produce the recombinant P6 protein. Further, it is not readily apparent that the laboratories followed the suggestion of Anilionis et al. This is also not persuasive because it is noted that the claims are drawn to a plasmid, expression in a lipidated form is a property of a vector in a specific host cell and not a structural property of the claimed plasmid. Further, there is no evidence of record that the plasmid combinations are not functional

for the intended use. Again the claims are not drawn to methods of producing large quantities of the protein. Applicants argue that there is no reasonable expectation of success. This is not persuasive, the art has successfully produced recombinant lipidated P6 using a plasmid based expression system. Applicants argue that potential to considerably improve the expression of heterologous genes does not provide a reasonable expectation of success and is merely an invitation to experiment. This is not persuasive, absolute predictability of success is not the standard for obviousness and because the art as combined, teaches that regulated strong promoters are preferred because of their properties and that this finding was echoed in the secondary references, there would have been a reasonable expectation of success. Furthermore, there would have been a reasonable expectation of success with the combinations, given the success of the substituted promoters at successfully producing mammalian genes, which the art teaches as more complicated. Given the successful production of lipidated P6 by the art, one of skill in the art would have a reasonable expectation of success in the production of lipidated P6 protein using the promoters taught by the art as combined.

The rejections are maintained.

New Rejections

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims have been amended to recite "the recombinant PAL, under the control of said promoter is expressed in lipidated form and yields that are higher than those expressed by a recombinant PAL that is not under the control of a tightly regulated promoter." The specification lacks basis for this concept in the specification as filed.

The degree of expression is related to the host cell system and not the plasmid per se. Therefore, Applicants are improperly combining different concepts of the structure of the claimed plasmid with the function in a host cell system. For example, the specification specifically notes that the same plasmid pPX4020 produce increased levels of rP6 protein expression in the *E. coli* strain BL21 and BLR, with the highest levels in the strain BLR. Therefore, the same promoter, in the same plasmid, produces different levels of the same recombinant PAL using different host cells. Thus, the now recited concept is described in the specification as related to selection of host cells and not to a direct comparison of the same PAL using different promoters. Further, the language of the claims is such that it allows for comparison of different PAL proteins with each other. The recitation of "the recombinant PAL" lacks antecedent basis in the claim and therefore it is not clear what this refers to. Even if one were to read this as referencing the recitation of "encoding a peptidoglycan-associated lipoprotein (PAL), then the latter recitation of " a recombinant PAL" allows for comparison to any other protein because "a" means any. This specification does not set forth a comparison with all things held constant except for the promoter, the now recited lipidated form and degree of yield as set forth in the claims. Applicants are mixing and matching independent concepts in the specification that provides for a new concept that has no basis in the written description of the specification as filed.

This issue is best resolved by Applicants pointing to the specification by page and line number where explicit or implicit written description support for this concept can be found.

Status of Claims

Claims 1-8 stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy

Primary Examiner

Art Unit 1645